UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides
and
Toxic Substances

MEMORANDUM

January 15, 2002

TXR#: 0050298

SUBJECT:	**MOLINATE** - Submission by California Rice Commission Re: Review of Reproductive Toxicity of Molinate
TO:	Wilhelmena Livingston Reregistration Branch, SRRD (7508W)
FROM:	Linda L. Taylor, Ph.D. Reregistration Branch I Health Effects Division (7509C)
THRU:	Whang Phang, Ph.D. Branch Senior Scientist, Reregistration Branch I Health Effects Division (7509C)

Submitter:	California Rice Commission
Molinate Registrant	Syngenta Crop Protection, formerly Zeneca Ag Products
Chemical:	S-ethyl hexahydro-1H-azepine-1-carbothioate
Synonym:	Molinate, Ordram
Caswell No.:	444
PC Code:	041402
DP Barcode:	D279392
Submission:	S606618
Action Requested:	Review.

INTRODUCTION: The California Rice Commission [CRC] has submitted [November 21, 2001] a review of the reproductive toxicity of Molinate compiled by Dr. Wilkinson. CRC considers the document "a comprehensive review of the research of Dr. Miller and others that supports the rat-specific hypothesis."

In their detailed review of the non-rodent studies, CRC judged three of the four rabbit studies to be insufficient to evaluate effects on rabbit fertility and male reproductive toxicity potential; the four rabbit studies showed no consistent pattern of results. Also, CRC states in the discussion section that together, the studies do provide "some information on problems which may affect study interpretation." It was concluded that the increase in pre-implantation loss observed in three of the rabbit studies was an equivocal effect due to design deficiencies and the inherent variability of this parameter in rabbits.

With respect to the dog data, the CRC review concludes that the data "are not considered to provide any reliable information regarding the potential for molinate to affect sperm parameters in dogs."

With respect to the monkey, one study was considered to have important deficiencies, including the lack of evaluation of epididymal sperm and histopathology of the testes. The other study was considered to have "several weaknesses in the study design which limit its usefulness." Additionally, only males were exposed to Molinate.

The CRC concludes that there is no persuasive scientific evidence that Molinate causes adverse reproductive effects in non-rodent species [rabbits, dogs, or monkeys]. RRBI has evaluated the CRC submission, and the following discussion contains our assessment of this submission.

DISCUSSION: The toxicology database indicates that in evaluating the reproductive effects of Molinate, study design is pivotal. Despite the acknowledged inadequacy of the available data, the CRC concludes that adverse reproductive effects are not likely in the non-rodent. How much confidence can one place on the lack of an observed effect when the study design is inadequate? HED has reviewed these studies in detail but could not discuss them in any detail in the Risk Assessment document since (1) they were not definitive studies with respect to fertility assessment and (2) the Risk Assessment Document did not lend itself to this type of discussion. Reference was made to them from the standpoint that the apparent effects observed could not be ruled out, in part because of the deficiencies and, in the case of the dog, the study was not designed to assess reproductive effects. It should also be pointed out that previously submitted data on metabolism in the dog indicate a similarity to that in the rat; i.e., approximately 30% of the administered dose was reported to be metabolized *via* sulfoxidation. Therefore, if the testicular effects were due to the Molinate sulfoxide, the dog would also be susceptible. Additionally, in a study in monkeys [MRID 42582301], 10% of a single oral dose of 60 mg/kg was eliminated as Molinate mercapturate, one of the sulfoxidation pathway metabolites.

Scientifically, use of inadequate data for the assessment of a particular effect to demonstrate the lack of toxicity is invalid.

The HED conclusion is that these data are insufficient to evaluate Molinate's reproductive toxicity potential in the non-rodent species. The overall conclusion is that reproductive effects in the non-rodent cannot be ruled out based on the available data. Because the rat appears to be the most susceptible species for reproductive effects, the rat data will continue to be used for risk assessment.

The required guideline studies that are available in the dog do not directly assess reproductive effects, Again, these and other reasons are the basis for HED overall conclusion that reproductive effects in the non-rodent cannot be ruled out based on the available data.

Another issue in the current submission is the Registrant's hypothesis to explain the mechanism of reproductive toxicity in rodents and its lack of relevance to humans. CRC believes that the Agency is being overly conservative and unrealistic in its expectations that the Registrant provide a precise, unambiguous mechanistic explanation of Molinate's action. HED disagrees with this assertion. While the proposed mechanism is biologically plausible, there are major discrepancies, conflicting information, and a lack of data to support what is being proposed. For example, contrary to the Registrant's opinion that the data currently available [DP Barcode D268066; Submission S583623] allow for the direct comparison of the extent of sulfur oxidation following exposure to Molinate in rat and man at comparable doses, RRBI believes the data/study referenced for man do not provide an assessment at the **1 mg/kg** dose level. The reference cited for the human data [Krieger, H., Fong, S., Frederickson, B., *et al.* (1992). Metabolite Metabolism Differs Substantially in Humans and Rats. The Toxicologist 12, 126] states that "a series of self-administrations of molinate were performed using the oral (0.03-0.7 mg/kg or 0.09-0.86 mg/cm^2) and dermal (0.06-0.6 mg/kg) routes." It further states that Molinate mercapturate was rapidly eliminated in urine, but it "only constituted 1-2% of the **dosage (0.03-0.1 mg/kg).**" Metabolism data on humans submitted to date by the Registrant [MRID 42582302] were from a study at a dose level of 5 mg [a single oral dose of 5 mg; 70-103 kg; 0.05-0.07 mg/kg]. Based on MRID 42582302, this reviewer believes the dose reported in the abstract is in error; the human dose was ≤ **0.1** mg/kg. Additionally, in the available metabolism study in humans, 4-hydroxy Molinate conjugate [39%] was the major metabolite found in urine and ≈ 1% was Molinate mercapturate [a metabolite in the sulfoxidation pathway]. **It is to be noted that greater than 50% of the administered dose in the human study was unaccounted for, and only two metabolites were monitored.** In light of the fact that cysteine conjugate [metabolite XIII in the sulfoxidation pathway] accounted for a substantial proportion of the urinary metabolites in the dog, the lack of an assessment of this metabolite in the human study is considered a deficiency. Based on the available data, Molinate metabolism has not been demonstrated to be different between the rodent and the human.

Another source of confusion with the available information/data involves the following. In two previous submissions by CRC, work performed by Dr. Miller is referenced. In one is a statement that it is "possible that mechanism(s) other than inhibition of esterase activity may play a role in the decreased testosterone production seen after molinate sulfoxide." It is to be noted that the inhibition of the esterase enzyme is one of the main pieces of the hypothesis being proposed by the Registrant to support the "rodent-specific" reproductive effect; i.e., inhibition of the cholesterol esterase enzyme is proposed to inhibit cholesterol ester hydrolysis and decrease the availability of cholesterol required for testosterone biosynthesis. The research results reported in the 2000 annual report suggest that the esterase inhibition may not be directly related to decreased testosterone synthesis. Additionally, during a teleconference with the researcher [December 12, 2001], Dr. Miller indicated that the literature regarding the Registrant's hypothesis that the rat uses HDL [high density lipoproteins] *vs* low density lipoprotein almost exclusively as the source of cholesterol is "murky", not definitive. The researcher also indicates that data to address the possibility that the source of cholesterol is different for the human *vs* the rat Leydig cell will not be available until 2002.

CONCLUSION: This review of the reproductive toxicity data by Dr. Wilkinson does not provide any new information to alter the HED position that Molinate produces fertility effects in the rat, and at this time, RRBI has not seen any data to indicate that these findings are not relevant to humans. Additionally, Dr. Wilkinson's conclusion that there is no persuasive evidence that Molinate causes adverse reproductive effects in non-rodent species [rabbits, dog, or monkey] is in direct conflict to his assertion that the data are insufficient to evaluate fertility effects and male reproductive toxicity potential in these species.